Pharmaco-informatics: More Precise Drug Therapy from "Multiple Model" (MM) Stochastic Adaptive Control Regimens: Evaluation with Simulated Vancomycin Therapy.

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ABSTRACT

MM stochastic control of dosage regimens permits essentially full use of information, either in a population pharmacokinetic model or a Bayesian updated MM parameter set, to achieve and maintain selected therapeutic goals with optimal precision. The regimens are visibly more precise than those developed using mean parameter values. Bayesian MM feedback has now also been implemented.

INTRODUCTION

In pharmaco-informatics, previous work showed the utility of NPEM population pharmacokinetic modeling, with discrete support points for the population joint probability density function. The points become multiple contending patient models to use to plan the initial MM dosage regimen for a new patient, and to update as feedback becomes available. We now describe a simulation of vancomycin therapy in which realistic errors are made in preparation and timing of doses, as well as in the measurement of serum levels.

METHODS

A 2 compartment population model of Vancomycin, previously developed using the NPEM2 program, had 28 support points, each of which had a value for each parameter, and its probability. Parameters were Vc, the apparent volume of the central (serum level) compartment, Kcp, the rate constant from central to peripheral compartment; Kpc, the reverse rate constant, and Kslope, the increment of elimination rate constant (Kel) for each unit of creatinine clearance (CCr). A nonrenal component, Kint, was fixed at 0.002043 hr^{-1}. A therapeutic goal of a stable serum vancomycin concentration of 15 ug/ml was chosen. Vancomycin was given by continuous IV in 3 infusion steps of 2 hrs each, followed by 3 steps of 6 hrs each, to achieve the goal of 15 ug/ml at the end of each infusion step.

The MM control strategy was evaluated by comparing it with conventional MAP Bayesian control, using a Monte Carlo simulation of a realistic clinical scenario containing errors in preparation (±10%) and timing (±12min) of the infusion steps, as well as serum assay error. Three days of therapy were simulated. Serum levels were "drawn" at 2, 4, and 8 hours into the regimen each day. Further, in a way that is never knowable clinically, the response of the simulated "true patient" (support point #15, chosen randomly), was also computed. The "true patient's" serum levels at 2, 4, and 8 hrs into the regimen were made available at the end of Day 1, and Bayesian updating was done. Therapy days 2 and 3 repeated the same scenario as Day 1.

RESULTS

The traditional MAP regimen, using mean population parameter values, was thus designed to achieve the goal of 15 ug/ml exactly. No consideration of therapeutic error was present. When that regimen was given to the 28 population support points, however, the serum level trajectories ranged from 9 to over 40 ug/ml, with 6 of the 28 trajectories (21%) being over 40 ug/ml.

In contrast, the MM regimen used all 28 support points of the Vancomycin population model instead of just the mean values, and computed the regimen to minimize the expected squared error in the achievement of the goal. The resulting 28 trajectories were much less variable, were better centered about the goal of 15 ug/ml, and ranged from 5 to 33 ug/ml.

The MM regimen thus delivered visibly greater precision than the traditional one. It used, for the first time, a real population pharmacokinetic model, that of Vancomycin. Further, the MM controller appeared to learn well from the feedback provided by the serum levels, and to control the simulated true patient well as it progressed from one feedback cycle to another. A user-friendly clinical version of the MM program is in development.

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